PATENT COOPERATION TREATY

RECEIVED
NOV 13 1996
SUSAN SESNOVICH

From the INTERNATIONAL SEARCHING AUTHORITY

To: PAUL T. CLARK
FISH & RICHARDSON, P. C.
225 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110-2804

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 00786/287W01	Date of Mailing *(day/month/year)* 06 NOV 1996
International application No. PCT/US96/12098	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant THE GENERAL HOSPITAL CORPORATION	International filing date *(day/month/year)* 22 JULY 1996

Docketed By Billing Secretary
Due Date:
Deadline:
Initials:

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

Docketed By Practice Asst.
Pct Search Report 1/6/97
Foreign Ant US1 2/6/97
Foreign Ant US2
97718, 97719, 97720

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHRISTOPHER S. F. LOW Telephone No. (703) 308-0196

Form PCT/ISA/220 (January 1994)*

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 00786/287W01	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US96/12098	International filing date *(day/month/year)* 22 JULY 1996	(Earliest) Priority Date *(day/month/year)* 21 JULY 1995
Applicant THE GENERAL HOSPITAL CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (See Box I).

2. [X] **Unity of invention is lacking** (See Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. ____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/12098

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 4-9
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 10-12, 29, 32, 37

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/12098

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07H 21/04; C12P 21/02, 19/34; C12N 15/85, 15/10, 5/10
US CL :536 / 23.5; 435 / 69.1, 91.1, 320.1, 172.3, 240.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536 / 23.5; 435 / 69.1, 91.1, 320.1, 172.3, 240.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Automated Patent System - USPAT and JPOABS
DIALOG - BIOSIS PREVIEWS, MEDLINE, Cancerlit
Search terms: hepadnavirus, receptor, duck, avian,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,675,285 A (CLARK et al.) 23 June 1987, see entire document.	1-2, 29, 32, 37
Y	PUGH et al. Characterization of a Pre-S polypeptide on the Surfaces of Infectioius Avian Hepadnavirus Particles. Journal of Virology. May 1987, Vol. 61, No. 5, pages 1384-1390, see entire document.	1-12, 29, 32, 37
Y	NEURATH et al. Detection of Receptors for Hepatitis B Virus on Cells of Extrahepatic Origin. Virology 1990, Vol. 176, pages 448-457, see entire document.	1-12, 29, 32, 37

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
24 OCTOBER 1996

Date of mailing of the international search report
06 NOV 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
CHRISTOPHER S. F. LOW
Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/12098

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KLINGMULLER et al. Hepadnavirus Infection Requires Interaction between the Viral Pre-S Domain and a Specific Hepatocellular Receptor. Journal of Virology. December 1993, Vol. 67, No. 12, pages 7414-7422, see entire document.	1-12, 29, 32, 37
Y	US 5,145,775 A (YAMADA et al.) 08 September 1992, see entire document and especially column 10.	1-12, 29, 32, 37
Y	US 5,149,781 A (BLAUDIN de THE et al.) 22 September 1992, see entire document.	1-12, 29, 32, 37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/12098

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

Claims 4-9 require a search of sequences 63-66, 74, 75 and of the sequence in the plasmid 69869. The computer form of the sequence was not present because of a virus on the submitted disk. Claims 6 and 8 require a search of the sequence of the DNA contained in the deposited plasmid 69869 but which sequence listing in the computer readable form is unavailable.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This International Search Authority has found 9 inventions claimed in the International Application covered by the claims indicated below:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-12, 29, 32, and 37 are drawn to a first product which is the DNA encoding hepadnavirus receptor polypeptide, vectors containing the DNA, and host cells containing the vector, a first process of use which is a process for producing the hepadnavirus receptor polypeptide, and a process for obtaining the DNA encoding the hepadnavirus receptor.

Group II, claim 13 is drawn to a second product which is the hepadnavirus receptor polypeptide per se.

Group III, claim(s) 17-22 and 28 are drawn to a third product which is a hepadnavirus pre S protein of nine amino acids and which is not the hepadnavirus receptor polypeptide.

Group IV, claim(s) 23-27 are drawn to a fourth product which is a polynucleotide encoding the hepadnavirus pre-S protein or fragments of the protein of nine amino acids.

Group V, claims 14 and 15 are drawn to a fifth product which is an antibody to the hepadnavirus receptor polypeptide.

Group VI, claim 16 is drawn to a sixth product which is a nonhuman transgenic animal which contains the hepadnavirus receptor polypeptide.

Group VII, claims 30, 31, and 33 are drawn to an alternative process of use which does not use the product of Group I and is a process of identifying an antagonist to the hepadnavirus receptor polypeptide by binding candidate ligands to the receptor.

Group VIII, claim 34-36 are drawn to alternative processes of use which is a method to reduce the level of hepadnaviral infection in an animal by treatment with an antibody or the pre-S protein fragment, or the nucleic acid encoding the

pre-S protein fragment.

The International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The claims of Group VIII indicate species which are an antibody or the pre-S protein fragment, or the nucleic acid encoding the pre-S protein fragment.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The Group VIII antibody, pre-S protein fragment and polynucleotide encoding the pre-S protein each have different chemical, physical, and biological properties and functions that do not overlap nor is any one of the antibody, pre-S protein fragment and polynucleotide encoding the pre-S protein a substitute for any one of the other species of antibody, pre-S protein fragment and polynucleotide encoding the pre-S protein.

The inventions listed Groups I through VIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I does not have the special technical features of Groups II, III, IV, or V since the DNA is not a protein nor does the DNA of Group I encode the pre-S protein or fragment thereof nor does it encode an antibody. Both the protein and the DNA can be produced by traditional chemical synthesis but which methods of synthesis employ different starting materials and produce different products with different physical, chemical, and biological properties. As to Groups I and IV, the polynucleotide encodes different proteins and the DNA in both Groups I and IV do not share the same sequence of bases. With regard to Group VI, the cells in Group nor the vectors nor the DNA per se are an intact multicellular animal nor do any of the claims in Group I require or use an intact animal. Thus, these groups do not share the same common special technical feature.

Group I does not share the same special technical feature as Groups VII and VIII since neither Group VII nor VIII use the product of Group I but use the products Group II through IV.

Group II does not share the same special technical feature as Groups III through VIII since hepadnavirus receptor polypeptide per se is not the same protein as the hepadnavirus pre S protein of nine amino acids nor is the receptor polypeptide a DNA encoding a peptide of residues which is a product with different physical, chemical, and biological properties from that of a DNA. Moreover, the Group II receptor is not an antibody (Group V) nor is the Group II

receptor per se a nonhuman transgenic animal. Group VII differs from Group II in the that receptor can be used in a process of making an antibody (Group V) and Group VIII is an alternative process of use of the product of Group II. Group III (a pre-S protein or fragment) does not share the same special technical feature as Groups IV through VI because Group IV is a polynucleotide and is not a polypeptide nor the pre-S protein, nor is the pre-S protein a antibody (Group V) or the transgenic animal (Group VI). Group III does not share the same special technical features since Groups VII and VIII and therefore, do not share the same special technical features.

Group IV (a polynucleotide encoding the hepadnavirus pre-S protein or fragments of the protein of nine amino acids) does not share the special technical feature of that of the Group V antibody to the hepadnavirus receptor polypeptide nor that of the Group VI nonhuman transgenic animal which contains the hepadnavirus receptor polypeptide. Groups VII and VIII are alternative processes of use of the product of Group IV and therefore do not share the same special technical features.

Group V, an antibody to the hepadnavirus receptor polypeptide does not share the same special technical features of the Group VI a nonhuman transgenic animal which contains the hepadnavirus receptor polypeptide and which does not contain the antibody. Group VII does not contain the same special technical feature as Group V since Group VII does not explicitly recite the antibody. Group VIII is an alternative process of use of the antibody

Group VI does not have the same special technical features of Groups VII or VIII since none of these groups indicate a transgenic nonhuman mammal or a process of using same.

Group VII, drawn to a process of use which identifies an antagonist to the hepadnavirus receptor polypeptide by binding candidate ligand to the receptor does not share the same special technical features as that of Group VIII which is an alternative process of use of the pre-S protein which does not indicate nor require finding an antagonist.